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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,085	07/23/2003	Sabine Gratzer	DEAV2002/0051US NP	5941

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EXAMINER	
JOIKE, MICHELE K	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,085	GRATZER ET AL.	
	Examiner	Art Unit	
	Michele K. Joike, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13 and 16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-13 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed August 16, 2006. Claims 1, 5 and 18 are amended. Claims 19-20 were added. Claims 2, 14, and 15 are canceled.

Claims 1, 3-13 and 16-20 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed February 27, 2006, that is not addressed in this action has been withdrawn.

Because this Office Action only maintains rejections set forth in the previous Office Action and/or sets forth new rejections that are necessitated by amendment, this Office Action is made FINAL.

Claim Objections

Claim 18 is objected to because of the following informalities: In claim 18, line 1, "modulates" has been changed to "molecules", which makes the preamble unclear. Appropriate correction is required.

Response to Arguments Concerning Claim Rejections – *35 USC § 102 (b)*

Applicants' arguments filed on August 16, 2006 have been fully considered. The following grounds of traversal are presented:

None of the references, Pausch, Crossin et al or Keating et al, teach use of a double reporter assay, and only disclose a single reporter assay.

Applicants' traversal has been fully considered and found to be persuasive in that neither Pausch or Crossin et al teach use of a double reporter assay. Keating et al teach a dual luciferase assay, however, they do not teach a dual reporter assay using two different reporters. Therefore, the 35 USC §102(b) is withdrawn. However, applicants' amendment has necessitated the new grounds of rejection under 35 U.S.C. 103(a) recited below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 12-13, 16-17 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch in view of US 6,063,578 and in further view of US 20050118690.

Applicant claims a method of identifying an agent that modulates the activity of a target molecule by contacting a cell with a candidate compound and modulating a target molecule, wherein said cell also comprises two reporter genes, a growth marker reporter and a reporter that is an enzyme or a fluorescent protein. After contact by agent, cell propagation and reporter activity are measured. The target molecule affects the reporter gene, wherein the target molecule is further limited to a heterologous molecule and can be a nucleic acid or polypeptide. The target molecule affects cellular propagation indirectly or through an intermediary molecule. The target molecule can also affect the reporter gene and cellular propagation directly. The reporter gene produces an enzyme that can be beta-galactosidase or luciferase. If the reporter is a fluorescent protein, it is GFP. The cell is a yeast cell, specifically *S. cerevisiae*.

Pausch (TIBTECH 15: 487-494, 1997, specifically Fig. 1b and p. 490) teaches a method of identifying an agent that modulates the activity of a target molecule by contacting a cell with a candidate compound and modulating a target molecule, wherein an agent, somostatin, modulates a target molecule, Sst2 (a heterologous receptor), which induces a FUS1-HIS3 reporter in a *S. cerevisiae* cell, causing expression of the HIS3 enzyme. Reporter activity is measured by growth on medium lacking histidine. A deletion of the FAR1 gene prevents cell cycle arrest, thereby affecting cell propagation. Sst2 activates a Map kinase pathway including Fus3, which activates FAR1. However,

FAR1 is deleted, so Sst2 affects cell propagation indirectly and through an intermediary molecule, Fus3. Fus3 is not able to activate FAR1, therefore there is cell growth. In another embodiment, Fus3 activates the FAR1 gene, which causes cell cycle arrest. However, deletion of the FAR1 gene prevents cell cycle arrest, therefore, Fus3 directly affects cell propagation. However, Pausch does not teach use of two reporters.

US 6,063,578 (specifically columns 8-10) teach a dual reporter assay. Two different reporters need to be used. Enzymatic and fluorescent proteins are taught. Specifically, beta-galactosidase, luciferase and GFP are taught. It also is stated that the precise reporter genes used are not critical as long as expression can be detected.

US 20050118690 (specifically paragraphs 92 and 93) teach a dual reporter assay for isolating transformants. US 20050118690 teach that it is preferable to have two reporter genes within the cell. One reporter gene, when expressed, provides a growth advantage to transformed cells that are expressing the variant regulator protein, like LEU2, HIS3, LYS2, TRP1, URA3 or ADE2. This allows for the isolation of such transformants though selective pressures. The other reporter gene provides a colorimetric marker, such as the lacZ gene and its encoded protein, beta.-galactosidase. Alternatively, the second reporter provides a fluorescent or luminescent marker, such as green fluorescent protein (GFP).

The ordinary skilled artisan, desiring to use a dual reporter system, would have been motivated to combine the teachings of Pausch teaching a method of identifying an agent that modulates the activity of a target molecule, which induces a reporter, with the teachings of US 20050118690 teaching a dual reporter system with LEU2, HIS3, LYS2,

TRP1, URA3 or ADE2 as the first reporter and lacZ or GFP as the second reporter, and with the teachings of US 6,063,578, teaching a dual reporter system because US 6,063,578, states that the dual reporter system allows for observation of more than one change induced by a candidate agent. For example, one reporter can indicate whether there is a change in replication, while the second reporter can indicate whether there is a change in transcription. It would have been obvious to one of ordinary skill in the art to use dual reporters because both processes occur on the same molecule, which more accurately reflects the natural environment. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 1, 5, 10-11 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crossin et al in view of US 6,063,578 and in further view of US 20050118690.

Applicant claims a method of identifying an agent that modulates the activity of a target molecule, wherein the agent contacts a cell and modulates the target molecule, and wherein said cell also comprises two reporter genes. After contact by agent, cell propagation and reporter activity are measured. The reporter genes produce a growth marker reporter and a reporter that is an enzyme. Measuring reporter activity comprises disrupting the cell by permeabilizing the membrane, or destroying the membrane. They also claim a second cell with a target molecule and reporter gene. After contact by agent, cell propagation and reporter activity are measured.

Crossin et al (PNAS 94: 2687-2692, 1997, specifically Abstract, Introduction, last paragraph, Exptl. Procedures, 2nd, 7th and last paragraph and Figure 4) teach a method of identifying an agent that modulates the activity of a target molecule by contacting a cell and modulating a target molecule, wherein an agonist, N-CAM, modulates a target molecule, GRE, which induces a luciferase reporter. N-CAM inhibits cell proliferation. In measuring luciferase activity, cells were lysed. They also teach a second cell with a second target molecule, CM-V and a second reporter beta-galactosidase. N-CAM is the agonist. However, Crossin et al do not teach the use of two reporters.

US 6,063,578 (specifically columns 8-10) teach a dual reporter assay. Two different reporters need to be used. Enzymatic and fluorescent proteins are taught. It also is stated that the precise reporter genes used are not critical as long as expression can be detected.

US 20050118690 (specifically paragraphs 92 and 93) teach a dual reporter assay for isolating transformants. US 20050118690 teach that it is preferable to have two reporter genes within the cell. One reporter gene, when expressed, provides a growth advantage to transformed cells that are expressing the variant regulator protein, like LEU2, HIS3, LYS2, TRP1, URA3 or ADE2. This allows for the isolation of such transformants though selective pressures. The other reporter gene provides a colorimetric marker, such as the lacZ gene and its encoded protein, beta.-galactosidase. Alternatively, the second reporter provides a fluorescent or luminescent marker, such as green fluorescent protein (GFP).

The ordinary skilled artisan, desiring to use a dual reporter system, would have been motivated to combine the teachings of Crossin et al teaching a method of identifying an agent that modulates the activity of a target molecule, which induces a reporter, with the teachings of US 20050118690 teaching a dual reporter system with LEU2, HIS3, LYS2, TRP1, URA3 or ADE2 as the first reporter and lacZ or GFP as the second reporter, and with the teachings of US 6,063,578, teaching a dual reporter system because US 6,063,578, states that the dual reporter system allows for observation of more than one change induced by a candidate agent. For example, one reporter can indicate whether there is a change in replication, while the second reporter can indicate whether there is a change in transcription. It would have been obvious to one of ordinary skill in the art to use dual reporters because both processes occur on the same molecule, which more accurately reflects the natural environment. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 1, 2-11 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keating et al in view of US 6,063,578 and in further view of US 20050118690.

Applicant claims a method of identifying an agent that modulates the activity of a target molecule wherein the agent contacts a cell and modulates the target molecule, and wherein said cell also comprises two reporter genes. After contact by agent, cell

propagation and reporter activity are measured. One of the reporter gene produces an enzyme, and the substrate of the enzyme is added after a delay, specifically at least one cell cycle. Measuring reporter activity comprises disrupting the cell by permeabilizing the membrane, or destroying the membrane.

Keating et al (Oncogene 20: 4281-4290, 2001, specifically Introduction, p. 4282 and Materials & Methods, 1st and 6th paragraphs) teach a method of identifying an agent that modulates the activity of a target molecule by contacting a cell and modulating a target molecule, wherein an agent, EGF, modulates a target molecule, ATM (a heterologous kinase), which induces a luciferase reporter. ATM is known to be involved in cell cycle control (see Abstract & Introduction). Cells were incubated with EGF for 16 hours before cells extracts were prepared. EGF was added during log phase, therefore at least one or two cell cycles have occurred. Firefly luciferase substrate (LARII) was added and reporter activity was measured using a Dual Luciferase Assay. However, Keating et al do not teach the use of two different reporters.

US 6,063,578 (specifically columns 8-10) teach a dual reporter assay, wherein two different reporters need to be used. Enzymatic and fluorescent proteins are taught. It also is stated that the precise reporter genes used are not critical as long as expression can be detected. Growth markers are not explicitly taught, however reporters, such as URA3, HIS3, and other growth markers are well known in the art. MPEP 2144.06 states that equivalents can be substituted as long as the equivalency is recognized in the art. HIS3 and URA3, for example, are well known in the art as common reporters.

US 20050118690 (specifically paragraphs 92 and 93) teach a dual reporter assay for isolating transformants. US 20050118690 teach that it is preferable to have two reporter genes within the cell. One reporter gene, when expressed, provides a growth advantage to transformed cells that are expressing the variant regulator protein, like LEU2, HIS3, LYS2, TRP1, URA3 or ADE2. This allows for the isolation of such transformants though selective pressures. The other reporter gene provides a colorimetric marker, such as the lacZ gene and its encoded protein, beta.-galactosidase. Alternatively, the second reporter provides a fluorescent or luminescent marker, such as green fluorescent protein (GFP).

The ordinary skilled artisan, desiring to use a dual reporter system, would have been motivated to combine the teachings of Keating et al teaching a method of identifying an agent that modulates the activity of a target molecule, which induces a reporter, with the teachings of US 20050118690 teaching a dual reporter system with LEU2, HIS3, LYS2, TRP1, URA3 or ADE2 as the first reporter and lacZ or GFP as the second reporter, and with the teachings of US 6,063,578, teaching a dual reporter system because US 6,063,578, states that the dual reporter system allows for observation of more than one change induced by a candidate agent. For example, one reporter can indicate whether there is a change in replication, while the second reporter can indicate whether there is a change in transcription. It would have been obvious to one of ordinary skill in the art to use dual reporters because both processes occur on the same molecule, which more accurately reflects the natural environment. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the

applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Allowable Subject Matter

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele K. Joike, Ph.D. whose telephone number is 571-272-5915. The examiner can normally be reached on M-F, 9:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michele K Joike, Ph.D.
Examiner
Art Unit 1636